

Bolus-Dose Vasopressors in the Emergency Department: First, Do No Harm; Second, More Evidence Is Needed

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Hypotensive patients in the emergency department (ED) represent some of the sickest patients. A predictor of poor outcomes, hypotension has been posited as a marker for shock and, in some cases, as the defining characteristic of shock.¹⁻³ Even as little as 10 minutes of hypotension has been associated with poor outcomes in high-risk patients.⁴ Noting this, some have postulated that treating even transient hypotension may stave off poor outcomes.

Enter the concept of bolus-dose vasopressors (commonly known as “push-dose pressors”). Bolus-dose vasopressors refer to the intravenous administration of small discrete doses of ephedrine, phenylephrine, or epinephrine to treat hypotension in lieu of or before vasopressor infusion. In the ED, because of their shorter duration of action, bolus-dose vasopressors typically refer to either phenylephrine or epinephrine. There is a significant body of evidence in the anesthesia literature supporting their safety and use in the operating room,⁵ although much of this literature concerns the use of phenylephrine for hypotension that develops during spinal anesthesia. There is great hypothetical appeal about the notion of drugs that can be rapidly mixed and administered to treat hypotension as it occurs.

In this issue of *Annals*, Holden et al¹ introduce safety considerations and guideline-based recommendations for the use of bolus-dose vasopressors in the ED. Although literature on the use of bolus-dose vasopressors in the ED is still in its infancy, they advocate a “systems-based” approach to balance patient safety and benefits. Their article also raises the question of whether social media has encouraged the use of bolus-dose vasopressors in the ED ahead of sufficient supporting evidence.

In this editorial, I will place the article by Holden et al in historical and clinical context by examining the establishment of similar clinical approaches in emergency medicine, suggesting the role social media appears to be

playing in knowledge translation, reviewing the existing clinical literature in regard to bolus-dose vasopressors, and evaluating the risks of physician medication delivery in high-risk situations. The first priority when one uses a therapy such as bolus-dose vasopressors that has limited supporting evidence needs to be “do no harm.”

In theory, the migration of bolus-dose vasopressors from the operating room to the ED seems natural; similar practice migration has served emergency medicine well in the past. In the 1980s, emergency physicians began using succinylcholine and other neuromuscular blockers to bring the practice of rapid sequence induction from the operating room to the ED to optimize intubating conditions for critically ill patients.⁶ This practice was initially met with resistance⁷ and even outright criticism of our specialty’s airway skills.⁸ Proponents of rapid sequence induction in the ED subsequently performed rigorous clinical research demonstrating superior outcomes for patients undergoing the procedure in the ED.⁹ Now rapid sequence induction is a cornerstone of the practice of emergency medicine.¹⁰

The use of propofol for procedural sedation has a similar history. In the 1990s, emergency physicians first reported the use of propofol in the ED,¹¹ which, despite early promising results,¹² was met with skepticism from both anesthesiologists and emergency physicians.¹³ Detractors cited specialty jurisdiction and the potential for respiratory depression and aspiration. Rigorous clinical trials of propofol for procedural sedation in the ED soon followed,^{14,15} demonstrating that it was safe and effective. Now propofol for sedation in the ED has become a mainstay of practice.¹⁶

Recently, new forces have propagated the rapid spread of clinical concepts: social media and free open access medical education.^{17,18} These forces may facilitate the spread of best practices; however, with inadequate editorial oversight research may also be translated too quickly through social media, leading to compromised outcomes when preliminary findings are incomplete or incorrect.¹⁹ This

stands in contrast to the decades during which propofol and neuromuscular-blocking agents gained popularity in emergency medicine. With the encouragement of social media and free open access medical education, the practice of using bolus-dose vasopressors in the ED has apparently become common, despite little published peer-reviewed evidence to support its use.

Currently, only 2 studies, both retrospective, address the use of bolus-dose vasopressors in the ED.^{20,21} Both demonstrate results that should give us pause. Panchal et al²⁰ analyzed 20 intubated hypotensive patients who received bolus-dose phenylephrine for peri-intubation hypotension. They found that bolus-dose phenylephrine was associated with an increase in blood pressure, with no change in pulse rate. Fourteen of these patients also received continuous infusions of other vasopressors. No other clinically meaningful outcomes were assessed. Schwartz et al²¹ assessed the frequency with which patients began receiving a continuous infusion of a vasopressor after receiving bolus-dose phenylephrine in their ED, with a secondary analysis of assessment of adequate preload expansion through crystalloid bolus. Of 73 patients receiving bolus-dose phenylephrine, 34 began receiving a continuous vasopressor infusion within 30 minutes. Only 34% of these 73 patients received an adequate fluid challenge; receiving one was associated with fewer doses of phenylephrine. Schwartz et al²¹ found the overall rate of serious adverse events associated with bolus-dose phenylephrine to be 20%, including bradycardia (10%), reactive hypertension (8%), and ventricular tachycardia (3%).

Safety considerations concerning the preparation and administration of these drugs compound the lack of positive evidence. In many cases, bolus-dose vasopressor administration is presumed to indicate a pharmacy- or manufacturer-prepared syringe. In this case, the concentration of the syringe, and by extension the dose of the drug, is inherent to the entire resuscitation team as there is no opportunity for a dilution to cause a 10-fold dosing error. Some proponents of bolus-dose vasopressors, however, advocate a practice by which the emergency physician draws up and dilutes a dose of epinephrine immediately before administration.²² This practice, which is not addressed by the 2 small ED studies on bolus-dose vasopressors, introduces a complicated task performed at a time (during active resuscitation of a critically ill patient) that is almost certainly highly stressful. The introduction of a dilution step into the preparation of epinephrine is not trivial; epinephrine has a storied history of 10-fold dosing errors harming patients.²³ If small bolus doses of epinephrine are needed immediately, using a “cardiac epinephrine” syringe (0.1 mg/mL, formerly

known as 1:10,000 concentration) to administer bolus doses eliminates the dilution step and may minimize risk. This manufacturer-prepared syringe allows rapid administration of very small doses (50 µg, or 0.5 mL).

The ability of physicians to perform dose calculations, particularly under stress, is worth examining. Emergency physicians, surgeons, and pediatricians have all been demonstrated to perform poorly when quizzed on dose calculations associated with simple medication vials.²⁴⁻²⁶ Newly certified physicians and physicians working in community practice are at higher risk for making dosing errors.²⁷ In regard to physicians’ making their own diluted push-dose epinephrine, this suggests that senior physicians in teaching positions may have a lower risk of making dilution-related dosing errors than newer physicians working in community practices. The inherent stress of the resuscitation complicates this matter further.²⁸ Performing mathematical tasks under pressure reveals that stress has a negative influence on mathematical problem solving.²⁹ This effect is mitigated if the specific mathematical task is practiced; however, significant practice is required.²⁹ It is easy to see how a less-experienced physician working in community practice who has only watched an instructional video on the proper dilution of epinephrine would be prone to making dosing errors. Even an experienced physician likely requires significant deliberate practice to avoid the same error.

The use of both neuromuscular blockers and propofol in emergency medicine was initially met with harsh criticism. Over time, evidence mounted that the use of these medications in the ED was safe and, according to clinically meaningful outcomes from high-quality research, improved on previous approaches. The use of bolus-dose vasopressors in the ED should inspire similar practice-changing research. Future research should examine whether treatment with a vasopressor leads to improved outcomes after transient hypotension in the ED, such as hypotension occurring after intubation or sedation. For patients in whom it is agreed that hypotension should be treated, randomized trials comparing the initiation of vasopressor infusions with or without the preceding use of bolus-dose vasopressors and measuring patient-centered outcomes such as mortality, hospital length of stay, and rates of medication errors would help define the role of bolus-dose vasopressors in the ED.

As it achieves popularity ahead of supporting science and literature, the practice of using bolus-dose vasopressors in the ED needs a framework to keep patients safe. Holden et al offer an approach that takes into account the difficulty of dose calculations and drug dilution under pressure. It is an important first step.

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REFERENCES

- Holden D, Ramich J, Timm E, et al. Safety considerations and guideline-based safe use recommendations for “bolus- dose” vasopressors in the emergency department. *Ann Emerg Med.* 2017; <http://dx.doi.org/10.1016/j.annemergmed.2017.04.021>.
- Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation.* 2011;123:1788-1830.
- Samant SA, Campbell RL, Li JT. Anaphylaxis: diagnostic criteria and epidemiology. *Allergy Asthma Proc.* 2013;34:115-119.
- Manley G, Knudson MM, Morabito D, et al. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Arch Surg.* 2001;136:1118-1123.
- Mohta M, Harisinghani P, Sethi AK, et al. Effect of different phenylephrine bolus doses for treatment of hypotension during spinal anaesthesia in patients undergoing elective caesarean section. *Anaesth Intensive Care.* 2015;43:74-80.
- Roberts DJ, Clinton JE, Ruiz E. Neuromuscular blockade for critical patients in the emergency department. *Ann Emerg Med.* 1986;15:152-156.
- Bessen HA, Rothstein RJ. NMB usage survey. *Ann Emerg Med.* 1986;15:1251-1252.
- Poulton TJ. Neuromuscular blocking agents in the ED. *Ann Emerg Med.* 1987;16:727-729.
- Tayal VS, Riggs RW, Marx JA, et al. Rapid-sequence intubation at an emergency medicine residency: success rate and adverse events during a two-year period. *Acad Emerg Med.* 1999;6:31-37.
- American College of Emergency Physicians. ACEP clinical and practice management: rapid-sequence intubation. Available at: <https://www.acep.org/Clinical—Practice-Management/Rapid-Sequence-Intubation/>. Accessed April 28, 2017.
- Swanson ER, Seaberg DC, Mathias S. The use of propofol for sedation in the emergency department. *Acad Emerg Med.* 1996;3:234-238.
- Havel CJJ, Strait RT, Hennes H. A clinical trial of propofol vs midazolam for procedural sedation in a pediatric emergency department. *Acad Emerg Med.* 1999;6:989-997.
- Green SM. Propofol for emergency department procedural sedation—not yet ready for prime time. *Acad Emerg Med.* 1999;6:975-978.
- Miner JR, Biros M, Krieg S, et al. Randomized clinical trial of propofol versus methohexital for procedural sedation during fracture and dislocation reduction in the emergency department. *Acad Emerg Med.* 2003;10:931-937.
- Burton JH, Miner JR, Shipley ER, et al. Propofol for emergency department procedural sedation and analgesia: a tale of three centers. *Acad Emerg Med.* 2006;13:24-30.
- Godwin SA, Burton JH, Gerardo CJ, et al. Clinical policy: procedural sedation and analgesia in the emergency department. *Ann Emerg Med.* 2014;63:247-258.
- Scott KR, Hsu CH, Johnson NJ, et al. Integration of social media in emergency medicine residency curriculum. *Ann Emerg Med.* 2014;64:396-404.
- Hayes BD, Kobner S, Trueger NS, et al. Social media in the emergency medicine residency curriculum: social media responses to the Residents’ Perspective article. *Ann Emerg Med.* 2015;65:573-583.
- Chan T, Trueger NS, Roland D, et al. Evidence-based medicine in the era of social media: scholarly engagement through participation and online interaction. *CJEM.* 2017;12:1-6.
- Panchal AR, Satyanarayan A, Bahadir JD, et al. Efficacy of bolus-dose phenylephrine for peri-intubation hypotension. *J Emerg Med.* 2015;49:488-494.
- Schwartz MB, Ferreira JA, Aaronson PM. The impact of push-dose phenylephrine use on subsequent preload expansion in the ED setting. *Am J Emerg Med.* 2016;34:2419-2422.
- Weingart S. Push-dose pressors for immediate blood pressure control. *Clin Exp Emerg Med.* 2015;2:131-132.
- Edgar TA, Lee DS, Cousins DD. Experience with a national medication error reporting program. *Am J Hosp Pharm.* 1994;51:1335-1338.
- Rolfe S, Harper NJ. Ability of hospital doctors to calculate drug doses. *BMJ.* 1995;310:1173-1174.
- Potts MJ, Phelan KW. Deficiencies in calculation and applied mathematics skills in pediatrics among primary care interns. *Arch Pediatr Adolesc Med.* 1996;150:748-752.
- Nelson LS, Gordon PE, Simmons MD, et al. The benefit of houseofficer education on proper medication dose calculation and ordering. *Acad Emerg Med.* 2000;7:1311-1316.
- Wheeler DW, Wheeler SJ, Ringrose TR. Factors influencing doctors’ ability to calculate drug doses correctly. *Int J Clin Pract.* 2007;61:189-194.
- Hunziker S, Laschinger L, Portmann-Schwarz S, et al. Perceived stress and team performance during a simulated resuscitation. *Intensive Care Med.* 2011;37:1473-1479.
- Beilock SL, Kulp CA, Holt LE, et al. More on the fragility of performance: choking under pressure in mathematical problem solving. *J Exp Psychol Gen.* 2004;133:585-600.